

REMARKS

I. The Rejection Under 35 U.S.C. §103(a) Should Be Withdrawn.

On page 2 of the Office Action, the Examiner has maintained the rejection of claims 1-7, 18, and 19 under 35 U.S.C. §103(a) as being allegedly unpatentable over Muller *et al.*, U.S. Patent No. 6,020,358 (“Muller”) in view of Tobinick, U.S. Patent No. 6,428,787 (“Tobinick”), and D’Amato, U.S. Patent No. 6,235,756 (“D’Amato”). Specifically, the Examiner has alleged that the instant claims are obvious because: (1) Muller allegedly “show[s] that the claimed compound is a TNF alpha blocker or inhibitor;” (2) Tobinick allegedly “show[s] the use of TNF inhibitors for the treatment of disorders such as macular degeneration;” and (3) D’Amato allegedly “show[s] that the claimed secondary components, such as thalidomide have been used for treating macular degeneration.” (Office Action, page 2). Applicant respectfully traverses this rejection.

The current standard of obviousness takes into account (1) whether there would have been a “reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does;” and (2) whether the combination of elements would have yielded “predictable results” *i.e.*, whether there would have been a reasonable expectation of success. (*See e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d at 1342, 1360 (Fed. Cir. 2007) (“The burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so.”) (emphasis added, internal quotations omitted)).

With regard to the instant case, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness. Specifically, Applicant respectfully submits the following:

- (1) The cited references would not have provided any reason to select the claimed compound for the treatment of macular degeneration; and
- (2) The cited references would not have provided the legally required reasonable expectation of success.

1. The cited references would not have provided any reason to select the claimed compound for the treatment of macular degeneration.

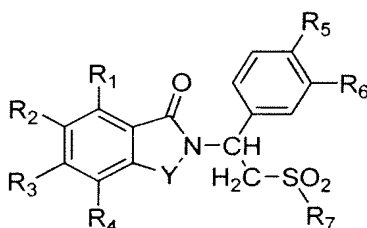
The Examiner's rejection is flawed because it relies on the false assumption that Muller actually discloses cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisindoline-4-yl}carboxamide ("the instant compound").

Indeed, the instant compound is not disclosed as an individual species in Muller.

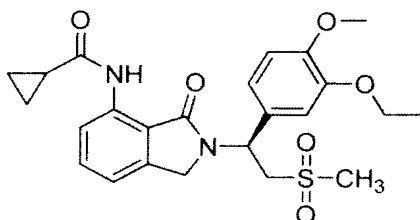
Further, the genus recited in claim 1 of Muller encompasses thousands of compounds and does not clearly suggest the instant compound.

To the extent the Examiner is relying on the genus recited in claim 1 of Muller, the rejection is improper because to arrive at the instant compound, one skilled in the art would have had to take the following steps: (1) select the appropriate variable values for Y and R¹-R⁹ from a large number of possible variables; (2) make the necessary structural modifications to R¹⁰; and (3) select the S isomer. (*See e.g., Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.* 492 F.3d 1350 (C.A.Fed. (N.Y.)), 83 U.S.P.Q.2d 1169 (Fed. Cir. 2007) ("[I]t remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.")).

Specifically, Muller recites the following broadly-defined genus in claim 1:



The structure of the instant compound is:



Thus, to arrive at the instant compound, one skilled in the art would have had to:

- (1) select CH_2 for \mathbf{Y} from a list of $\text{C}=\text{O}$, CH_2 , and $\text{CH}_2\text{C}=\text{O}$;
- (2) select $-\text{NR}^8\text{R}^9$ for \mathbf{R}^1 from a list of hydrogen, halo, alkyl of 1-4 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxy, $-\text{NR}^8\text{R}^9$, or, taken together with an adjacent R^2 , R^3 , or R^4 , naphthylidene;
- (3) select H for \mathbf{R}^2 from a list of hydrogen, halo, alkyl of 1-4 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxy, $-\text{NR}^8\text{R}^9$, or, taken together with an adjacent R^1 , R^3 , or R^4 , naphthylidene;
- (4) select H for \mathbf{R}^3 from a list of hydrogen, halo, alkyl of 1-4 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxy, $-\text{NR}^8\text{R}^9$, or, taken together with an adjacent R^1 , R^2 , or R^4 , naphthylidene;
- (5) select H for \mathbf{R}^4 from a list of hydrogen, halo, alkyl of 1-4 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxy, $-\text{NR}^8\text{R}^9$, or, taken together with an adjacent R^1 , R^2 , or R^3 , naphthylidene;
- (6) select alkoxy of one carbon for \mathbf{R}^5 from a list of hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cyano, or cycloalkoxy of up to 18 carbon atoms;
- (7) select alkoxy of two carbons for \mathbf{R}^6 from a list of hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cyano, or cycloalkoxy of up to 18 carbon atoms;
- (8) select alkyl of 1 carbon for \mathbf{R}^7 from a list of hydroxy, alkyl of 1-8 carbon atoms, phenyl, benzyl, or $-\text{NR}^{8'}\text{R}^{9'}$, wherein each of $\text{R}^{8'}$ and $\text{R}^{9'}$ taken independently of the other is hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl, or one of $\text{R}^{8'}$ and $\text{R}^{9'}$ is hydrogen and the other is $-\text{COR}^{10'}$, or $-\text{SO}_2\text{R}^{10'}$, or $\text{R}^{8'}$ and $\text{R}^{9'}$ taken together are tetramethylene, pentamethylene, hexamethylene, or $-\text{CH}_2\text{CH}_2\text{X}^2\text{CH}_2\text{CH}_2-$ in which X^2 is $-\text{O}-$, $-\text{S}-$ or $-\text{NH}-$;
- (9) select H for \mathbf{R}^8 from a list of hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, benzyl, $-\text{COR}^{10}$, $-\text{SO}_2\text{R}^{10}$, or, taken together with R^9 , tetramethylene, pentamethylene, hexamethylene, or $-\text{CH}_2\text{CH}_2\text{X}^1\text{CH}_2\text{CH}_2-$, in which X^1 is $-\text{O}-$, $-\text{S}-$ or $-\text{NH}-$;

(10) select COR¹⁰ for R⁹ from a list of hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, benzyl, -COR¹⁰, -SO₂R¹⁰, or, taken together with R⁸, tetramethylene, pentamethylene, hexamethylene, or -CH₂CH₂X¹CH₂CH₂, in which X¹ is -O-, -S- or -NH-;

(11) make structural modifications to arrive at cyclopropyl for R¹⁰ because cyclopropyl is not specifically listed as a possible variable¹; and

(12) select the (S) isomer.

However, nothing in Muller would have given any reason to specifically select the variable values above for Y and R¹-R⁹ from the large number of possibilities. Further, nothing in Muller would have provided any insight as to the desirability of making the structural modifications necessary to arrive at cyclopropyl for R¹⁰. In this regard, to the extent the Examiner is relying on allegations of structural similarity as a basis for the rejection, such a rejection is improper because allegations of structural similarity have been flatly rejected by the courts as a basis for determinations of obviousness.

For example, in *Takeda*, even though the Federal Circuit acknowledged that a known compound's homologs, analogs, or isomers "often have similar properties" and that chemists may "contemplate making them to try to obtain compounds with improved properties," the Court nonetheless emphasized that "in order to find a *prima facie* case of unpatentability in such instances, a showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention [is] also required." (*Id.* at 1356) (internal citations omitted) (emphasis added)). Indeed, the Court cautioned "that generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other." (*Id.* at 1361 (quoting *In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985))). Thus, the current law of obviousness in cases concerning structurally similar compounds "requires a showing of 'adequate support in the prior art' for the change in structure." (*Id.* at 1356 (quoting *In re Grabiak*, 769 F.2d at 729)). As the Court stated:

in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a

¹ Applicant acknowledges that Muller discloses alkyl of 1 to 8 carbons as possible variable values for R¹⁰ and that a cyclopropyl group is an alkyl group. However, even if cyclopropyl is considered an alkyl group, the Examiner has not pointed to any teaching that would have provided any insight as to the desirability of (1) picking a substituent with 3 carbons; and (2) picking a cyclic alkyl group (as opposed to a non-cyclic alkyl group).

particular manner to establish prima facie obviousness of a new claimed compound.

(*Id.* at 1357 (emphasis added)).

With regard to the step of selecting the (S) isomer, the Federal Circuit specifically addressed the issue of whether a single enantiomer of a compound can be nonobvious in view of a prior art disclosure of that compound's racemate and affirmed the patentability of chiral pharmaceutical compounds. (*See Forest Labs., Inc. v. Ivax Pharmaceuticals, Inc.*, 501 F.3d 1263 (Fed. Cir. 2007), *aff'g* 438 F.Supp.2d 479; also *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); and *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, 348 F.Supp.2d 713, 755 (N.D.W.Va. 2004)). It is also well known to those of ordinary skill in the chemical and pharmaceutical arts that the separation and/or preparation of specific isomers is not predictable, nor are these processes always routine. (*Id.* at 493; *see also* J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, 2007 Stanford Tech. L. Rev. 2, ¶56 ("the process for making the racemate may not make obvious a process for resolving the racemate.")). Further, whether a specific stereoisomer has improved biological activity or a more desirable pharmacological profile is recognized as unpredictable in the art. (*See In Re May* at 1092; *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, at 754 (the prior art suggested unpredictability in the degree of activity exhibited by a specific enantiomer); *see also Ex Parte Bonfils*, 64 U.S.P.Q.2d 1456, 1461 (B.P.A.I. 2002)).²

Muller provides no preference for the biological or pharmacological activity of the racemic compound, much less any indication of the activity of the specific (S)-isomer for treating macular degeneration within the instant claims. Without such specific guidance in the cited art, one of ordinary skill in the art would not have had any reason to select the specific (S)-isomer recited in the instant claims. Without such a reason, a *prima facie* case of obviousness cannot be made. (*See KSR*, 127 S.Ct. at 1742; *Takeda*, 429 F.3d at 1359.) Thus, even assuming, *arguendo*, that one of ordinary skill in the art would have selected the racemate of the recited compound, Applicant respectfully submits that the instant claims, which specifically recite the (S)-isomer for treating macular degeneration, are not obvious by Muller.

Further, even assuming, *arguendo*, that the instant compound is encompassed by the genus recited in claim 1 of Muller, Applicant respectfully submits that the Examiner does not

² *Bonfils* is a nonprecedential decision.
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appear to appreciate that this genus is broadly defined and encompasses thousands of compounds. As well settled, the legally required “reason” to select a species or subspecies from a genus for purposes of 35 U.S.C. §103 does not exist unless there was “[s]ome motivation to select the claimed species or subgenus [from] the prior art.” (*In re Deuel*, 51 F.3d 1552, 1558-9, 34 USPQ2d 1210 (Fed. Cir. 1995) (“No particular one of these DNA’s can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared.”) (emphasis added); *In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994) (“Absent anything in the cited prior art suggesting which of the 10³⁶ possible sequences corresponds to [a gene], the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences.”); *see also* MPEP §2144.08). This principle has not changed after the *KSR* decision, as evidenced by the Federal Circuit’s decision in *Takeda*. (492 F.3d at 1350). In *Takeda*, the Court held that it was not obvious to select one compound out of a prior art reference that disclosed a large amount of compounds, in part, because “[r]ather than identify predictable solutions...the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation.” (*Id.* at 1359 (emphasis added)).

In the instant case, similar to *Takeda*, “rather than identify predictable solutions,” Muller discloses a genus that encompasses a large number of compounds, “any one of which could have been selected as a lead compound for further investigation.” (*Id.*). Moreover, similar to *Baird*, “[a]bsent anything in the cited prior art suggesting which of the [many] possible [compounds] corresponds to [the claimed compound],” the PTO has not met its burden of establishing that the prior art would have suggested the [claimed compound].” (*Baird*, 16 F.3d at 380). As such, even if the instant compound were encompassed by the genus of Muller, it would not have been obvious to select the compound. Indeed, the fact that Muller discloses a broad genus alone renders the Examiner’s rejection under 35 U.S.C. §103 improper.

Tobinick and D’Amato do not cure the defects of Muller because nothing in these references would have given any reason to specifically select variable values for Y and R¹-R⁹ required to arrive at the instant compound from the large number of possibilities. Further, nothing in Tobinick or D’Amato would have provided any insight as to the desirability of making the structural modifications necessary to arrive at cyclopropyl for R¹⁰, nor any insight as to the desirability of specifically isolating the (S)-isomer.

Significantly, the Examiner appears to acknowledge that Tobinick and D'Amato were actually not relied upon to show the instant compound; rather “Tobinick is used to show the use of TNF inhibitors for the treatment of disorders such as macular degeneration” and “D'Amato was cited to show that the claimed secondary components...have been used for treating macular degeneration.” (Office Action, page 2). Thus, the Examiner appears to allege that Muller alone “show[s] that the claimed compound is a TNF alpha blocker or inhibitor.” (*Id.*). However, as discussed, Muller would not have provided any reason to make or use the instant compound, much less show it has TNF α activity.

While the Examiner has alleged on page 2 of the Office Action that Tobinick “teaches thalidomide, a small molecule as TNF inhibitor,” such an allegation would not have provided a legally sufficient reason to make and use the instant compound for purposes of 35 U.S.C. §103(a). First, as discussed above, allegations of structural similarity have been flatly rejected by the courts as a basis for a determination of obviousness. (*Takeda*, 492 F.3d at 1356.) Second, as shown in Figure 1 below, the structures are not even similar. One skilled in the art, from merely looking at the structure of thalidomide, would not have been provided any insight as to the desirability of, for example, (1) removing the 1-oxo group from the isoindolinyl group; (2) completely replacing the piperidine 2,6-dione substituent with a 1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl substituent; or (3) adding a cyclopropylcarboxamide group. Nor does the structure of thalidomide suggest the desirability of isolating the (S) isomer. Indeed, as shown below in Figure 1, the chemical structures are radically different.

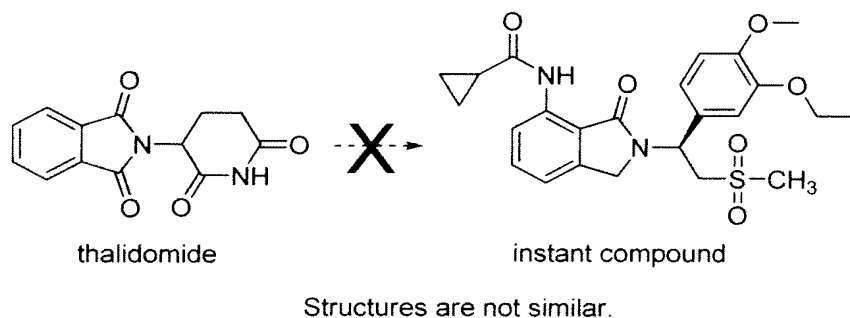


Figure 1. Structure of thalidomide and claimed compound.

Next, even assuming, *arguendo*, that Muller does teach or suggest the instant compound is a TNF α inhibitor, nothing in the cited references would have provided a reason to specifically single out macular degeneration. While the Examiner has alleged on page 2 of

the Office Action that Tobinick “show[s] the use of TNF inhibitors for the treatment of macular degeneration,” a broad genus of TNF-related disorders is disclosed. For example, Tobinick notes that “[t]hese disorders are diverse” and include among others:

inflammatory and autoimmune disorders of the nervous system, including multiple sclerosis, Guillain Barre syndrome, and myasthenia gravis; degenerative disorders of the nervous system, including Alzheimer’s disease, Parkinson’s disease and Huntington’s disease; disorders of related systems of the retina and of muscle, including optic neuritis, macular degeneration, diabetic retinopathy, dermatomyositis, amyotrophic lateral sclerosis, and muscular dystrophy; and injuries to the nervous system, including traumatic brain injury, acute spinal cord injury, and stroke.

(Tobinick, column 2, lines 29-39). Yet the Examiner has failed to explain how Tobinick, Muller, or D’Amato would have provided a reason to single out macular degeneration from these disorders. For this reason alone, the Examiner’s rejection under 35 U.S.C. §103(a) should be withdrawn.

In sum, to arrive at the instant claims, in skilled in the art would have had to take the following steps:

- (1) select the proper values for Y and R¹-R⁹ from the large number of possible values for the genus recited in claim 1 in Muller;
- (2) select cyclopropyl for R¹⁰;
- (3) specifically select the (S) isomer; and
- (4) specifically select macular degeneration from the large list of disorders disclosed in Tobinick.

However, as discussed, the Examiner has not pointed to any portion in the cited references that would have hinted the desirability of performing any of these steps. Thus, those skilled in the art at the time of the invention, who do not have the benefit of hindsight, would not have had any reason to carry out the steps to arrive at the instant claims. Since such a reason

is legally required for establishing a *prima facie* case of obviousness, the Examiner's rejection should be withdrawn.³

2. The cited references would not have provided the legally required reasonable expectation of success.

The Examiner has failed to explain how one skilled in the art would have had a reasonable expectation that the claimed compound would be effective in treating macular degeneration. The Federal Circuit, following *KSR*, articulated guidelines for determining "whether the expectation of success from a particular line of inquiry is great enough to render a resulting invention obvious." (*PharmaStem*, 491 F.3d at 1364). As the Federal Circuit explained:

[A]n invention would not be invalid for obviousness if the inventor would have been motivated to **vary all parameters or try each of numerous possible choices** until one possibly arrived at a successful result, where the prior art gave either **no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful**. Likewise, an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

(*Id.* (citing *In re O'Farrell*, 953 F.2d 894, 903 (Fed. Cir. 1988))(internal quotations omitted) (emphasis added)).

In the instant case, to arrive at the instant compounds, not only would one skilled in the art have had to "try each of numerous possible choices" of variables from the genus of Muller⁴, but one skilled in the art would have also have had to "try each of numerous possible choices" of TNF-related disorders from Tobinick. Yet none of the cited references would have provided any "indication of which parameters were critical" or any "direction as to which of [the] many possible choices is likely to be successful." As is evident from *PharmaStem*, this scenario is exactly what the Federal Circuit warned is **not** a legally

³ Claims 2-5 recite the use of the instant compound in combination with a second active component. Since Applicant has shown that a *prima facie* case of obviousness has not been established with respect to the claims reciting the use of the claimed compound, a *prima facie* case of obviousness with respect to claims 2-5 has also not been established. The Examiner alleges that D'Amato "was cited to show that the claimed secondary components, such as thalidomide have been used for treating macular degeneration." (Office Action, page 2). However, even taking this allegation to be true, as discussed above, none of the cited references would have hinted the desirability of the instant compound in the first place.

⁴ As well as make structural modifications with respect to R¹⁰ and specifically select the (S) isomer.
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sufficient “reasonable expectation of success.” (*Id.*). The combination of references, at most, would have merely provided general guidance and would have merely provided a list of many disorders and a list of many compounds – none of which is actually the instant compound – without any indication as to why the instant compound would be specifically useful for the claimed disorder. Thus, the cited references do not provide the requisite expectation of success, and the rejection should be withdrawn.

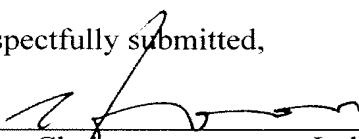
II. Conclusion

For at least the foregoing reasons, Applicant respectfully submits that all of the pending claims are allowable, and thus, requests that the rejections be withdrawn.

No fee is believed due for the submission of this paper. However, if any fees are due for the submission of this paper or to avoid abandonment of this application, please charge them to Deposit Account No. 50-3013.

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Respectfully submitted,


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